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Investigation of the relationship between early pregnancy losses and urinary iodine concentration

Early pregnancy and urinary iodine

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Abstract
Aim: The aim of this study was to evaluate the relationship between the development of spontaneous abortion (SpA) and hypothyroidism developing during pregnancy in patients who were euthyroid before pregnancy.
Material and Methods: This prospective study included 44 women with singleton pregnancies with a history of pregnancy loss and 43 women with singleton pregnancies with no history of loss. All patients were in the first 12 weeks of pregnancy. Age, gestational age, number of miscarriages, gravida, body mass index, free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulant hormone (TSH), and urinary iodine concentration levels (UIC) were measured. Parameters were compared between the groups using the independent samples t-test. Correlation analysis was performed to determine relationships between the parameters in the groups. The Pearson correlation coefficient was calculated. A value of $p<0.05$ was considered statistically significant.
Results: The mean UIC (145.3±56.01 µg/L) in the SpA group was lower than in the non-abortus group (186.9±68.80 µg/L) ($p= 0.001$). In the SpA group, there more hypothyroidic patients, and FT4 values were statistically significantly low ($p=0.004$). Correlation analysis determined a significant correlation between UIC and SpA ($r: -0.438^*$, $p<0.001$). As a result of the binary logistic regression analysis, recurrent SpA and moderate and severe iodine deficiency were seen to have contributed to the development of SpA in the current pregnancy.
Discussion: The results of this study showed that even in patients who were euthyroid before pregnancy, with the increasing iodine requirement in pregnancy, iodine deficiency can emerge and this can cause hypothyroidism and increase the risk of the development of SpA.

Keywords
Abortion, Iodine, Thyroid Hormones, Pregnancy

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Introduction

Spontaneous abortion (SpA), also called miscarriage, is one of the most common pregnancy complications, and is associated not only with morbidity or mortality [1], but also has important social and psychological impacts on women [2]. The incidence of SpA has been reported to be as high as 15%, and at least 80% of these events occur in the first trimester of pregnancy [3]. Advanced maternal age and previous SpA are among the risk factors for the development of SpA [4, 5].

Hypothyroidism in pregnancy is known to be associated with SpA, low birth weight, reduced cognitive functions, and an increased rate of stillbirths [6]. Maternal thyroid hormones are of vital importance especially in the early weeks of pregnancy because of the risk of underdevelopment of fetal thyroid tissue, and deficiencies can cause SpA. As a result of this increased requirement for thyroid hormone, the need for maternal iodine shows an increase by more than 50% in pregnancy [6].

Several recent studies have shown that pregnancies may be at risk of mild iodine deficiency, not only in iodine-deficient regions, but also in regions where iodine is sufficient. These studies have also emphasized that hypothyroidism can develop without any known thyroid pathology associated with the need to meet the increased requirement in pregnancy [7, 8]. However, to date, there has been no evaluation of the relationship between maternal iodine status and hypothyroidism developing in pregnancy and the occurrence of SpA in patients who were euthyroid before pregnancy.

Therefore, the aim of this study was to evaluate the relationship between the development of SpA and hypothyroidism developing during pregnancy in patients who were euthyroid before pregnancy.

Material and Methods

The study was conducted between April 2018 and July 2018 in the gynecology and obstetrics clinic of a second-level state hospital. Approval for the study was granted by the Ethics Committee of Yıldırım Beyazıt University, Yenimahalle Education and Research Hospital (decision no: 2018/01). All included patients were informed in writing about the study. Written consent was obtained from those who agreed to participate in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. In order to determine the sample size, a power analysis was performed using G * Power software. To obtain a power of 0.80 and α error of two-way 0.05, it was determined that the lowest number of patients to be included was a total of 90 patients as 45 patients in the SpA group and 45 patients in the non-SpA group. The effect width was calculated to be at least 0.80, and the power of the study over this effect width was determined as 95%.

The study included patients with no thyroid nodules observed ultrasonographically before pregnancy and normal thyroid hormone levels (45 SpA patients) and a control group of 45 age and gestational week-matched patients with no SpA.

To exclude factors that may affect urinary iodine concentration (UIC), patients with diabetes mellitus diagnosed before pregnancy, chronic hypertension, liver disease, kidney disease, heart disease, or a cancer diagnosis were excluded from the study. To exclude factors that may cause SpA, pregnant women with uterine anomalies, previous uterine surgery, or chronic drug use were also excluded from the study. Those with hypertension, gestational diabetes mellitus, heart disease, or fetal anomaly detected on ultrasonography were not included in the study. None of the study participants were taking multivitamins or iodine supplements during pregnancy. Pregnant women with thyroid dysfunction who were diagnosed before pregnancy or who had to be diagnosed and used medication during pregnancy and/or patients with autoimmune thyroid disease or nodule detected ultrasonographically were excluded from the study. All pregnant women were measured hemogram, fasting blood glucose, liver function tests, renal function tests, Toxoplasma IgG, IgM, Rubella IgG, IgM, and VDRL. The blood samples of 3 pregnant women (1 in the SpA group and 2 in the non-SpA group) were found to be hemolysed, and these patients were excluded from the study. A 5 mL urine specimen routinely collected at -20°C was collected from all the study participants who were admitted to the gynecology outpatient clinic and were healthy in the first 12 weeks of gestation. The study group comprised 44 pregnant women who underwent clinical examination and were determined with SpA or without fetal cardiac activity on ultrasonographic examination up to the 12th week. The control group comprised 43 pregnant women with fetal cardiac activity at the end of the 12th week. Age, gravida, gestational week, number of spontaneous abortions, body mass index (BMI) were recorded, as well as the values of the routinely studied free T3 (FT3), free T4 (FT4), total thyroid-stimulating hormone (TSH) levels, and hemoglobin and fasting blood glucose (FBG) levels. The flow chart of the study is shown in Figure 1.

Biochemistry

The previously collected spot urine samples were stored at -20°C and then brought to room temperature for assay when the number of patients required was met. Using urine brand colorimetric method / Italy kit, the urine iodine level was examined in the 5 mL urine samples of each patient. By drawing a graph, the 405 nm (nanometer) absorbance and calibrator values were calculated. The UIC values for pregnant women defined by the World Health Organisation (WHO) are adequate iodine=median UIC of 150–249 μg/L, mild iodine deficiency (ID)=UIC of 100–150μg/L, moderate and severe ID=UIC<100 μg/L, and excessive iodine = UIC ≥250 μg/L.

Statistical Analysis

Data obtained in the study were analyzed statistically using the SPSS vn. 22 software (Statistical Package for the Social Sciences). Conformity of the data to a normal distribution was assessed with the Shapiro-Wilk test, and a normal distribution of variables in the groups was found. Parametric tests were used to analyze the data. To compare parameters between these two groups that are homogeneous and have non-homogeneous data, the Independent Samples t-test and the Mann-Whitney U test were used. To examine correlation coefficients between the examined parameters, correlation analysis was applied to both groups and the Pearson correlation coefficients were calculated.

A value p<0.05 was considered statistically significant.

Results

The demographic variables of the patients evaluated in this study are shown in Table 1 and Figure 1. No difference was determined between the groups in respect of demographic variables such as age and gestational week (p>0.05 for all). Multiparity and ≥1 miscarriage were determined at a statistically significant higher rate in the SpA group (p=0.035, p<0.001, respectively).

Thyroid hormone levels and UIC values of the patients were compared (Table 2). The thyroid hormone levels were classified taking the ranges in the test kit as a reference. FT4 values were determined to be below the normal reference value in 27.3% of the SpA group patients and in 7% of the non-SpA control group (p=0.004). High TSH values consistent with hypothyroidism were determined in 20.4% of the SpA group and in 4.7% of the control group (p=0.023).

The median UIC values of the SpA group (145.38±56.01) were statistically significantly lower than those of the control group (186.95±68.80) (p<0.001) (Figure 2). When the UIC values were evaluated with subgroup analysis, moderate and severe ID was determined in 15.9% of the SpA group and in 2.3% of the control group. Mild ID was determined in 54.6% of the SpA group and in 23.3% of the control group. The difference between the groups in respect of the UIC values was statistically significant.

When the factors related to the development of SpA were evaluated, the strongest relationship was seen to be the development of SpA in a (≥1) previous pregnancy (r: 0.545, p<0.001). A strong negative correlation was determined between the development of SpA and UIC values (r:-0.438, p=0.001). The factors related to SpA are shown in Table 3.

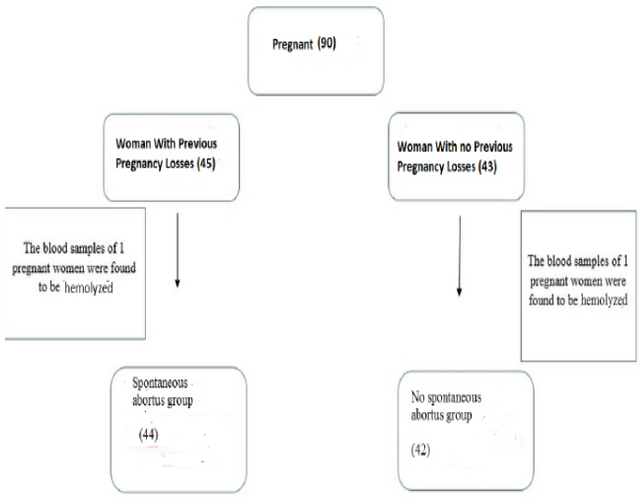

Figure 1. Flow chart of patient selection

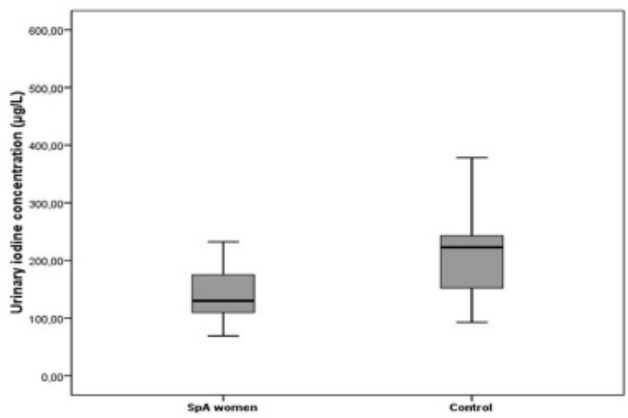

Figure 2. Mean urinary iodine concentration values of the patients in the study and control groups.

Table 1. The demographic variables of the patients in both groups

Variables		SpA women (n=44)	non-SpA women (n=43)	p
Age (year)		32.4±5.7	31.9±4.9	0.865
Gestational age (week)		7.43±1.6	7.39±1.9	0.924
Gravida		2.4±1.2	1.9±1.1	0.085
Parity number (%)	Nulliparity	9 (20.4%)	21 (48.8 %)	0.035
	Multiparity	35 (79.6 %)	22 (51.2 %)	
Number of SpA number (%)	0	0 (0 %)	34 (79.1 %)	<0.001
	1	37 (84.1 %)	4 (9.3 %)	
	Recurrent (≥2)	7 (15.9 %)	5 (11.6 %)	
BMI (kg/m2)		24.1±3.3	23.2±3.6	0.223
Smoking, n %		11 (25.0 %)	7 (16.3 %)	0.272

Table 2. The thyroid hormone values and urinary iodine concentration values of the patients before pregnancy and during the study

Variables		SpA women (n=44)	non-SpA women (n=43)	p
The thyroid hormone values before pregnancy				
TSH level range: 0.27–4.2 mIU/L		2.32±1.27	2.24±1.24	0.780
FT4 level range: 0.85–1.7 ng/dl		1.42±0.45	1.45±0.55	0.800
FT3 level range: 2.04–4.4 ng/L		2.89±0.78	3.04±0.92	0.613
The thyroid hormone values during pregnancy				
TSH level range: 0.27–4.2 mIU/L		3.07±1.30	2.39±1.10	0.009
FT4 level range: 0.85–1.7 ng/dl		1.16±0.50	1.44±0.48	0.009
FT3 level range: 2.04–4.4 ng/L		2.24±0.82	2.77±0.65	0.001
TSH level range: 0.27–4.2 mIU/L	Low	0 (0 %)	3 (7 %)	0.023
	Normal	35 (79.5 %)	38 (88.3 %)	
	High	9 (20.5 %)	2 (4.7 %)	
FT4 level range: 0.85–1.7 ng/dl	Low	12 (27.3 %)	3 (7 %)	0.004
	Normal	29 (65.8 %)	28 (65.1 %)	
	High	3 (6.9 %)	12 (27.9 %)	
FT3 level range: 2.04–4.4 ng/L	Low	8 (18.2 %)	0 (0 %)	0.013
	Normal	35 (79.5 %)	42 (97.7 %)	
	High	1 (2.3 %)	1 (2.3 %)	
UIC1		145.38±56.01	186.95±68.80	0.001
UIC, <100 µg/L2		7 (15.9 %)	1 (2.3 %)	
UIC, 100–150µg/L2		24 (54.6 %)	10 (23.3 %)	
UIC, 151–249 µg/L2		10 (22.7 %)	24 (55.8 %)	
UIC, ≥250 µg/L2		3 (6.8 %)	8 (18.6 %)	

FT3: serum concentrations of free triiodothyronine (ng/dl); FT4: serum concentrations of free thyroxine (ng/dl); SpA women, women after spontaneous abortion; TSH, serum concentrations of thyroid-stimulating hormone (mIU/l); UIC, urinary iodine concentration (µg/L); p, level of significance. 1 Expressed as mean ±standard deviation. 2 Expressed as number (%). UIC, (<100 µg/L2); moderate and severe ID. UIC, 100–150µg/L2; mild ID, UIC, 151–249 µg/L2; adequate iodine, UIC, ≥250 µg/L2; excessive iodine

Table 3. Evaluation of the factors affecting the development of SpA and results of binary logistic regression analysis of factors associated with SpA

	Spontaneous abortion	
	r	p
Presence of previous abortion	0.545**	<0.001
TSH level	0.292**	0.006
FT3 level	-0.275*	0.010
FT4 level	-0.352**	0.001
Urine iodine level	-0.438*	<0.001
Variable	**OR (95% CI)**	**p**
Urinary iodine concentration (Ref: moderate and severe ID)	1.065 (1.024-1.283)	0.019
Recurrent SpA (Ref: (≥1))	1.249 (1.098-1.407)	0.005

Adjusted R^2 = 0.615 / p-value of the model's ANOVA <0.001, * Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed). CI, Confidence interval, OR, Odds ratio;

When the rates of the effect on SpA development of the factors showing a relationship in correlation analysis were evaluated with binary logistic regression analysis, it was determined that a history of SpA increased the probability of SpA development in the current pregnancy 1.249-fold (95% confidence interval: 1.098-0.0407, p=0.005). UIC was determined to be another factor affecting SpA development (odds ratio: 1.065, 95% CI: 1.024-1.283, p=0.019). The analysis results are shown in Table 3.

Discussion

SpA is a common complication occurring in 1-2 % of pregnant women [9]. Inadequate maternal iodine stores during pregnancy cause insufficient thyroid hormone production, which has serious adverse effects on the fetus. The thyroid gland of a fetus is not completely functional until 12 weeks of gestation. Some studies have shown that subclinical maternal hypothyroidism increases early pregnancy losses and abnormal fetal development [10, 11], although conflicting results have been reported related to ID as a reason for fetal loss [12].

In a study from China that included 1569 previously euthyroid pregnant women in the ≤12th week of pregnancy, participants were separated into four groups based on the WHO criteria for iodine levels during pregnancy [9]. Post-pregnancy outcomes such as spontaneous abortion, gestational hypertension, pre-eclampsia, gestational diabetes mellitus, placenta previa, placental abruption, preterm delivery, low birthweight infants, macrosomia, breech presentation, and cord entanglement were followed. Both iodine insufficiency and excessive iodine intake in the first trimester were shown to have adverse effects on pregnancy outcomes [9].

In two older studies, it was shown that severe maternal ID increased neonatal deaths, recurrent miscarriages and early labour, and that outcomes improved with iodine supplementation [13, 14]. The prevalence of mild to moderate iodine deficiency in pregnant women is an important reason to determine whether iodine contributes to early pregnancy losses [15]. In a study that examined 171 patients with spontaneous abortion and normal thyroid function test results, ID was detected in >50% of the women [16]. In contrast, some studies have reported different results on this subject. A population-based, prospective, cohort study examined the urine iodine of 501 women planning to be pregnant within 2 months. Of these, 329 women became pregnant, and 196 had live births (59.5%), 92 (28.0%) experienced pregnancy loss, and 41 (12.5%) were withdrawn from the study or their data were not available. The UIC values of only 59.6% of the study participants could be determined. The risk of loss, however, was not elevated in the mildly deficient group (hazard ratio 0.69, 95% CI 0.34, 1.38), the moderately deficient group (hazard ratio 0.81, 95% CI 0.43, 1.51), or the severely deficient group (hazard ratio 0.69, 95% CI 0.32, 1.50). According to the results of that study, moderate ID and even at a severe level was not related to pregnancy loss [17]. In another study, UIC values were examined in 3140 singleton pregnancies and 42 patients with early pregnancy loss. Maternal mild or moderate ID was not found to be associated with adverse pregnancy outcomes [18].

In the current study, the UIC values of the pregnant women in the SpA group were determined to be significantly lower than those of the control group. However, there are specific boundary values in biochemical parameters, and if the results are within the normal range values, the individual is not negatively affected by the results. For more detailed clarification, in the current study, UIC values were classified according to the WHO values. Accordingly, moderate and/or severe deficiency was seen in 15.9% of the SpA group patients and as this rate was 2.3% in the control group, the difference between the groups was seen to be significant. In the correlation analysis, there was determined to be a significant relationship between low UIC values and the development of SpA. In the regression analysis, low UIC values were seen to increase the probability of SpA by 1.065-fold (95%CI 1.024-1.283).

Although the development of SpA is affected by many factors, these were excluded as far as possible by the extremely strict patient selection criteria of this study. For example, advanced maternal age has been shown to be directly associated with SpA as an important factor in many studies, but in the current study no relationship was determined with age. This can be attributed to the matching of patient age in the groups, as stated in the Materials and Methods section.

The most important limitation of the current study was the relatively low number of patients. However, the number was deemed to be sufficient according to the power analysis applied. The main factor preventing the inclusion of a greater number of patients was the exclusion of patients with known thyroid pathologies before pregnancy.

Conclusion

The results of the study clearly showed that when the increased need for iodine in pregnancy is not met in patients who were euthyroid before pregnancy, ID may emerge and this can cause hypothyroidism and increase the risk of SpA. This increased risk is even more important in recurrent miscarriages. Therefore, patients with a history of pregnancy loss must be clinically evaluated in respect of iodine status, even if they were euthyroid before the pregnancy, and patients determined with deficiency must be treated.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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